WHAT'S NEW *in the* MEDICINE CHEST?

An Update on the Latest Developments in

Nonsteroidal Topical Therapy for Atopic Dermatitis

This ongoing column explores emerging treatments, drug development trends, and pathophysiologic concepts in the field of dermatology.

ABSTRACT

The author provides a thorough review of the latest topical treatment approaches for atopic dermatitis. Some agents are currently available in the marketplace, while others are in development. Modes of action, including phosphodiesterase-4 inhibition, aryl hydrocarbon receptor activation, and Janus kinase inhibition are discussed. Emphasis is placed on therapeutic approaches related to modes of action, with clinical data included.

KEYWORDS: Atopic dermatitis, phosphodiesterase-4, crisaborole, aryl hydrocarbon receptor, Janus kinase inhibitors

by JAMES Q. DEL ROSSO, DO, FAAD, FAOCD

Dr. Del Rosso is Research Director at JDR Dermatology Research in Las Vegas, Nevada; is with Thomas Dermatology in Las Vegas, Nevada, and is an adjunct clinical professor of dermatology at Touro University Nevada in Henderson, Nevada.

J Clin Aesthet Dermatol. 2020;13(5):44–48

Atopic dermatitis (AD) is a common chronic and recurrent inflammatory skin disorder.[1–3] AD usually starts during infancy or in very early childhood, progresses through later childhood and adolescence with periods of exacerbation and relative remission, and can persist into adulthood, presenting as eczematous dermatitis, localized and/or diffuse, with a variety of clinical characteristics.[4,5] The variable clinical presentations of AD can include a broad range of diagnoses, such as chronic hand eczema, nummular eczema, prurigo nodularis, dyshidrotic eczema, eyelid dermatitis, lichen simplex, nipple eczema, and periumbilical pruritic papules.[4–6] Genetic predisposition is a major associated factor for the development of AD and other atopic disorders, such as asthma, allergic conjunctivitis, and seasonal rhinitis.[7] Importantly, AD is a heterogeneous disease state with multiple phenotypic expressions rooted in a multifactorial pathophysiology that are influenced by complex interactions between susceptibility genes, altered and impaired epidermal barrier function, environmental factors, variations in skin microbiologic flora (i.e., microbiome), and immunologic dysregulation involving multiple aspects and pathways of the immune system.[7,8] Extensive research on the pathophysiology and treatment of AD has become a major priority in dermatology, as gains in our understanding of the mechanisms of atopic disease are leading to major advances in therapy that are more targeted in their approach.[9–11]

This article reviews new and emerging nonsteroidal topical treatment approaches in AD, with emphasis on agents that reduce cutaneous inflammation via mechanisms beyond moisturization and barrier repair and maintenance.

TOPICAL PHOSPHODIESTERASE-4 (PDE4) INHIBITION

Phosphodiesterases (PDEs) are a group of ubiquitous intracellular enzymes that are physiologically involved in maintaining a variety

FUNDING: No funding was provided for this study.

DISCLOSURES: Dr. Del Rosso, in relation to this subject area, is an advisor, research investigator, and/or speaker for Almirall, Anaptys Bio, Arcutis, Botanix, Dermavant, Dermira (Lilly), Encore, Galderma, Incyte, La Roche Posay, LEO Pharma, MC2, Menlo Therapeutics, Ortho Dermatologics (Bausch), Pfizer, Ralexar, Regeneron, Sanofi/Genzyme, Sonoma, and Sun Pharma. He is the sole author of this article and has not received any form of compensation related to writing or publishing this article from any pharmaceutical or device company or from any of their affiliated agencies.

CORRESPONDENCE: James Q. Del Rosso, MD; Email: jqdelrosso@yahoo.com

of functional processes in many organ systems, such as modulation of inflammation, blood flow, and neurologic functions.[12] Phosphodiesterase-4 (PDE4) is found in a variety of cell types, including keratinocytes, inflammatory cells, and synovial cells, and converts cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP), with the relative balance between cAMP and AMP impacting directly on the expression of proinflammatory and anti-inflammatory mediators.[12,13]

Role of PDE4 in AD. The activity of PDE4 is a component of intracellular homeostatic balance that maintains normal physiologic function when operating without dysfunction. When cAMP levels are low, there is activation of nuclear factor kappa-B (NF-κB), which serves to increase proinflammatory cytokine production and suppress production of anti-inflammatory cytokines.[14,15] In AD, there is overexpression of PDE4 in cutaneous cells and in peripheral blood cells, which leads to increased conversion of cAMP to AMP; overexpression of AMP creates an imbalance that promotes inflammation through increased proinflammatory cytokine expression.[16–19]

Topical crisaborole for AD treatment. Crisaborole is a topically applied, low-molecular weight molecule with favorable penetration into skin that selectively targets and inhibits PDE4. This leads to decreased production of AMP and suppression of inflammation via decreased proinflammatory cytokine production.[16] Pharmacokinetic evaluation in pediatric and adult patients, including maximal use studies in pediatric cohorts, has demonstrated negligible systemic exposure; clinical studies have supported the absence of any systemic safety signals to date.[16,20–22] Efficacy was confirmed with crisaborole 2% ointment applied twice a day for mild-to-moderate AD in patients older than two years of age in the original pivotal studies, with reduction in pruritus also established, and with a *post-hoc* analysis showing efficacy and favorable safety in all races and ethnicities.[16,21–23]

New data on crisaborole mode of action (MOA) in AD. More recently, a study was completed to more specifically examine the MOA of crisaborole using gene expression profiling, biomarker evaluation through testing of messenger RNA (mRNA) expression, histologic examination, immunohistochemical staining to assess immune cell infiltration,

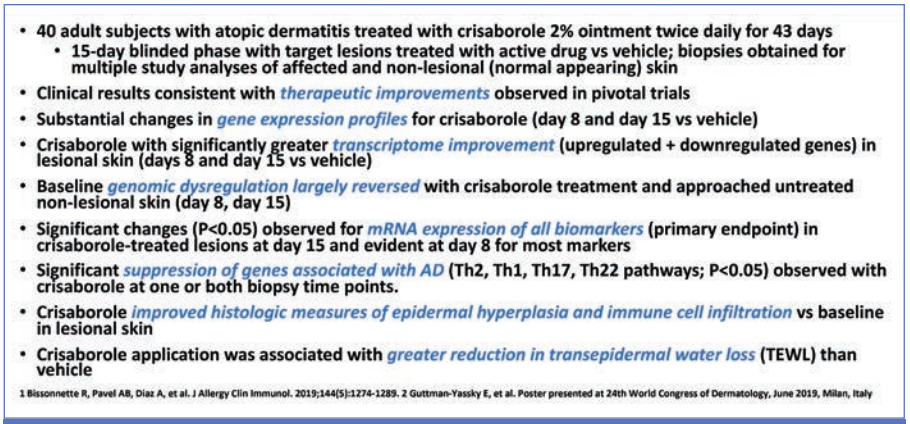

FIGURE 1. Crisaborole 2% ointment research support for modes of action in patients with atopic dermatitis; summary of study outcomes based on gene expression profiling, biomarker evaluation, histologic, and immune infiltrate analyses in patients with atopic dermatitis

and determination of impact on skin water content and flux (e.g., transepidermal water loss [TEWL]).[24,25] A Phase IIa, single-center, vehicle-controlled, intrapatient study was completed in adults (N=40) with mild-to-moderate AD. In randomized subjects, two target lesions were selected in an intrapatient (1:1) double-blind method to evaluate crisaborole 2% ointment versus vehicle ointment, each applied twice daily for 14 days to their respective target lesions; subsequently, crisaborole ointment was applied to all affected areas for 28 days in an open-label fashion. For biomarker analysis, punch biopsy specimens were obtained at baseline and Day 15, and were optional at Day 8 of the study.

Study outcomes revealed several observed changes in the affected areas treated with crisaborole, which support findings from other clinical studies that showed the therapeutic benefits of crisaborole 2% ointment (Figure 1).[24,25] Early improvement in lesional signs and symptoms of AD was noted with crisaborole versus vehicle, including reduction in pruritus as early as 24 hours after initial application. Based on results shown with genetic expression profiles, lesions treated with crisaborole demonstrated marked percentage improvement from baseline in lesional transcriptomic profiles, compared to vehicle, at Day 8 (91.15% vs. 36.02%, $P<0.05$), which were sustained until Day 15 (92.90% vs. 49.59%, $P<0.05$). From a clinical perspective, these results indicate application of crisaborole can convert the gene transcriptome profile associated with AD-affected skin to what is observed in normal-appearing (nonlesional) skin. Additionally, crisaborole application favorably modulated key AD biomarkers, compared to vehicle, including those reflecting the activity of T helper-2 (Th_2) and Th_{17}/Th_{22} pathways that are operative in AD pathophysiology. Epidermal hyperplasia/proliferation was also reduced more markedly in crisaborole-treated lesions. Molecular profiles and epidermal pathology showed reversal toward normal appearing skin and correlated directly with favorable visible changes in lesion severity and in measures assessing epidermal barrier function (e.g., reduction in TEWL) in crisaborole-treated lesions.[24,25]

Crisaborole use in younger pediatric populations. Prior to March 2020, crisaborole 2% ointment was approved by the United States (US) Food and Drug Administration (FDA) for topical treatment of mild-to-moderate atopic dermatitis in adult and pediatric patients two years of age or older. In a four-week clinical study in subjects ranging in age from three months to two years (median age 13 months), crisaborole 2% ointment applied twice daily was evaluated in subjects with mild-to-moderate AD affecting a mean body surface area of 28 percent.[26] Approximately 30 percent of enrolled subjects were 3 to 9 months of age (n=43), with a racial distribution of 60 percent White, 20 percent Asian, eight percent Black, and the remainder distributed among other racial designations, including multiracial (9.5%). Approximately 60 percent of subjects, two-thirds male sex, presented with moderately severe AD at baseline, assessed using Investigator Global Assessments (IGA) scale, with a mean onset of disease reported to be 10.2 months. Several exploratory endpoints were evaluated at Days 8, 15, and 9. Safety outcomes were consistent

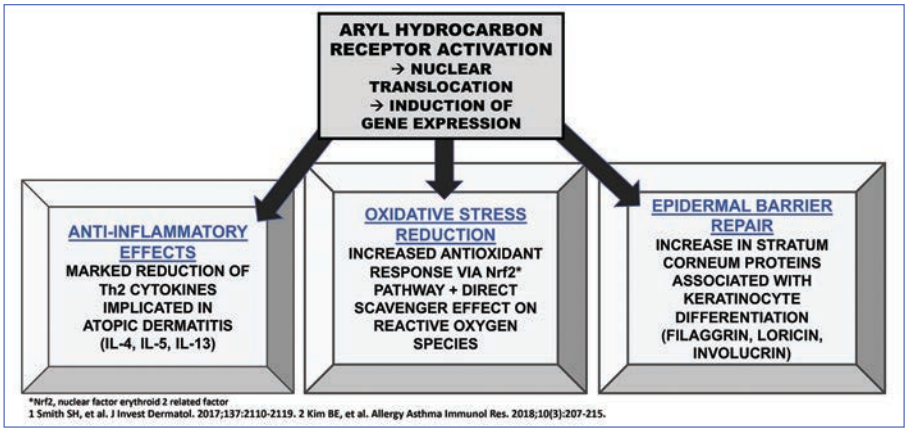

FIGURE 2. Modes of action of tapinarof in atopic dermatitis

with earlier pivotal trial findings, with no new or systemic safety signals reported and incidence of skin tolerability application site reactions similar to those reported in Phase III trials in subjects older than two years of age.[26] To summarize efficacy outcomes, progressive improvements in efficacy endpoints were noted throughout the study based on assessments at Days 8, 15, and 29. At the end of the study (Day 29), 47.3 percent of subjects were "clear" or "almost clear," based on IGA ratings, the mean percent reduction in Eczema Area Severity Index (EASI) was 57.53 percent, and the decrease in percent body surface area (BSA) affected was 15.24 percent.[26]

This study provides evidence supporting the efficacy and safety of crisaborole 2% ointment in patients under the age of two years (as young as 3 months) with mild-to-moderate AD. As of March 2020, crisaborole 2% ointment has been FDA-approved for twice-daily topical treatment of mild-to-moderate AD in adults and in children three months of age or older.

ARYL HYDROCARBON RECEPTOR (AHR) ACTIVATION

The aryl hydrocarbon receptor (AhR), a transcription factor found in multiple cell types, including keratinocytes, is capable of sensing and forming a ligand with environmental stimuli that can modulate inflammatory pathways that are likely to be operative in psoriasis and AD.[27,28] Specifically, AhR-activating ligands have been shown to reduce inflammation in psoriatic lesional skin, and AhR antagonists can augment inflammation.[28] Similarly, ligand-induced AhR signaling reduced the inflammatory response commonly observed in the imiquimod-induced skin inflammation model and in murine studies. AhR-deficient mice exhibited a marked exacerbation of inflammatory disease, compared to AhR-sufficient controls. Notably, keratinocytes were primarily responsible for this hyperinflammatory response associated with upregulation of AP-1 family members of transcription factors.[27] With regard to AD, in addition to evidence that AhRs modulate proinflammatory cytokine expression downstream in human skin and peripheral blood lymphocytes, AhRs also impact epidermal barrier gene expression in human keratinocytes.[28,29]

Role of AhR and MOA in inflammatory skin disease and AD. The aryl hydrocarbon receptor (AhR)/AhR-nuclear translocator (ARNT) system is a sensitive sensor for small molecular, xenobiotic chemicals of exogenous and endogenous origin, which provides some explanation for how certain exogenous agents, such as phytochemicals, microbial bioproducts, and tryptophan photoproducts, might contribute to skin inflammation.[29] There are several potential MOAs for inflammatory skin disease management associated with agonism of AhRs that facilitate AhR nuclear translocation, ultimately modulating proinflammatory gene expression.[28–30] These include the following (Figure 2):

- With high abundance in keratinocytes, the AhR/ARNT axis strengthens epidermal barrier function and integrity through acceleration of epidermal terminal differentiation and upregulation of filaggrin expression. Filaggrin contributes to structural integrity of the stratum corneum and is the source of natural moisturizing factor (NMF), which provides humectancy, supporting epidermal barrier function.
- Although AhR activation might induce oxidative stress, some AHR ligands simultaneously and paradoxically activate the nuclear factor-erythroid 2-related factor-2 (NRF2) transcription factor, which serves as a master switch of antioxidative enzymes that neutralize oxidative stress.
- AhRs have been shown to participate in the immunoregulation pathways of Th_{17}/Th_{22} cells and T regulatory (Treg) cells. AHR agonists, such as tapinarof, demonstrated anti-inflammatory effects in early efficacy studies in AD and psoriasis. Evidence to date suggests that the cytokine pathways regulated through AhR agonism are operative in the pathophysiology of both AD .

Clinical data with topical tapinarof in AD. Dose-ranging and dose-frequency evaluations of topical tapinarof cream have been studied. A double-blind, vehicle-controlled, six-arm, 12-week trial with even randomization (1:1:1:1:1:1) was completed in subjects with moderate (IGA 3) to severe (IGA 4) AD at baseline.[30] The age range of enrolled subjects was 12 to 65 years, with total BSA involvement of 5 to 35 percent. Primary endpoint success was measured as an IGA rating of "clear" or "almost clear" (0 or 1, respectively) and a minimum two-grade improvement at Week 12. Secondary analyses included a 75-percent-or-greater improvement in EASI score, reduction of numeric rating scale (NRS) score for itch from baseline, and other selected endpoints.

In the trial, 165 adult and adolescent subjects were actively treated with tapinarof cream and 82 were treated with vehicle. Rates of treatment success with tapinarof cream at Week 12 were 53 percent, 46 percent, 37 percent, and 34 percent with 1% twice daily, 1% once daily, 0.5% twice daily, and 0.5% once daily, respectively, and 28 percent and 24 percent with vehicle twice daily and once daily, respectively.[30] The rate with a concentration of 1% twice daily (53%) was statistically significantly higher than the rate with vehicle twice daily (24%). In addition, after treatment was stopped at four weeks, endpoint success with tapinarof treatment was sustained. Treatment-emergent adverse events (AEs), which were determined by investigators to possibly be related to study medication , were higher with tapinarof (56%) than with vehicle (41%), with the majority of AEs noted to be mild-to-moderate in intensity. The most common treatment-related AEs were folliculitis

(5% tapinarof vs. 0% vehicle) and application-site "pain" (i.e., stinging, burning) (1% tapinarof vs. 4% vehicle); no systemic safety signals were observed in any of the study subjects.[30]

Based on both basic science and clinical research, tapinarof will likely become a viable nonsteroidal topical treatment option for patients with AD, and possibly for patients with psoriasis.

JANUS KINASE INHIBITION

A variety of surface receptors found on multiple cell types are thought to possibly induce a broad range of physiologic responses, via binding to cytokines, including many that are involved with immunomodulation. Several of these Type I and Type II receptors depend on the interaction between Janus kinases (JAKs) and cytoplasmic signal transducer and activator of transcription proteins (STATs) for translocation from the cell membrane to the nucleus. This results in signal transduction that expresses specific gene proliferation profiles.[31–36] Ultimately, these JAK-STAT signaling pathways, including dimerization and phosphorylation, are used by a variety of cytokines (e.g., interleukins [ILs], interferons [IFNs]) to express specific biologic and cellular responses, such as Th_1, Th_2, Th_{17}, Th22, and several other profiles.[31–36] Dysfunctions within JAK-STAT signaling pathways can produce specific inflammatory and/or autoimmune reactions or disease states.

Role of JAK inhibitors in dermatology. At first glance, cellular overexpression analyses appear to suggest that JAKs indiscriminately signal many downstream cytokine receptors. However, it is now becoming apparent that cytokine receptors exhibit clear preferences of interaction among the JAK family members they utilize to effectuate signaling responses.[36] The designated interactions of specific receptors, JAKs, and STAT proteins, with specific cytokine response patterns, has led to the development of oral JAK inhibitors or "jakinibs" (JAK-Is) that, to date, have been FDA-approved for variety of disease states, such as rheumatoid arthritis, myelofibrosis, and polycythemia vera.[31–36] Both oral and topical JAK inhibitors show strong potential to become treatment for inflammatory and autoimmune skin disorders, such as psoriasis, AD, alopecia areata, and vitiligo.[36–46] Although published literature on topical JAK-Is are limited to date, there have been studies using topical JAK-Is for the treatment of AD.

Clinical studies with topical JAKs for AD. A double-blind, randomized, eight-week, dose-finding, Phase II study evaluated topical ruxolitinib (RUX) versus vehicle in adult subjects (N=307) with mild or moderate AD affecting 3- to 20-percent BSA.[45] Subjects were equally randomized to receive RUX 1.5% cream twice daily (BID), RUX 1.5% cream once daily (QD), RUX 0.5% cream QD, vehicle, or triamcinolone 0.1% cream BID for four weeks followed by vehicle BID for four weeks. In a subsequent open-label study, subjects could apply RUX 1.5% cream BID for an additional four weeks. The primary efficacy endpoint was mean percentage change from baseline in EASI in the RUX 1.5% cream BID arm versus the vehicle arm at Week 4. In all RUX-treated study arms, therapeutic benefit was noted at Week 4. Compared to vehicle, RUX 1.5% cream BID produced the greatest improvement in EASI (71.6% vs. 15.5%; $P<.0001$) and in overall clinical response based on IGA (38.0% vs. 7.7%; $P<.001$). In addition, RUX 1.5% cream BID produced rapid decreases in pruritus scores within 36 hours ($P< .0001$) which were sustained over the 12-week duration of therapy. In those subjects who transitioned to RUX 1.5% cream BID for the final four weeks of the study, improvements in AD were noted in all efficacy measures. No clinically significant application-site reactions or safety signals were reported.[45]

Tofacitinib formulated as a 2% ointment was investigated for topical treatment BID versus vehicle BID in a Phase IIa, randomized, double-blind, four-week study in adults (N=69) with mild-to-moderate AD.[46] Percentage change from baseline in EASI score at Week 4 was the primary endpoint, with other commonly assessed parameters defined as secondary efficacy endpoints. Safety and local skin tolerability were monitored over the duration of the study. The mean percentage change from baseline in EASI score at Week 4 was significantly greater ($P<0.001$) for tofacitinib (-81.7%) versus vehicle (-29.9%). Additionally, tofacitinib-treated subjects demonstrated significant improvements, compared to vehicle, across all defined efficacy endpoints and for pruritus at Week 4 ($P<0.001$), with reductions in pruritus noted by Day 2, and improvements in EASI, PGA and BSA observed by Week 1. Safety and local skin tolerability were favorable and generally similar in both study arms.[46]

CONCLUSION

With topical treatment remaining a central component of AD management, the development of new topical therapies for AD beyond the currently available topical corticosteroid formulations is important. Pathophysiology of AD is better understood due to advances in basic science research, and therapeutic agents that target different pathways involved in AD are beginning to emerge and be extensively studied. As new effective and safe therapies become available to treat this challenging chronic, recurrent disease, clinicians have more treatment options from which to choose, ultimately improving the care they provide their patients with AD, short term and long term, and patient outcomes.

REFERENCES

1. Pezzolo E, Naldi L. Epidemiology of major chronic inflammatory immune-related skin diseases in 2019. *Expert Rev Clin Immunol*. *Expert Rev Clin Immunol*. 2020 Feb;16(2):155–166.
2. Silverberg JI. Public health burden and epidemiology of atopic dermatitis. *Dermatol Clin.* 2017;35: 283–289.
3. Emanuel PO, Scheinfeld N, Williams HC. The epidemiology of atopic dermatitis. In: Rudikoff D, Cohen SR, Scheinfeld N, Eds. *Atopic Dermatitis and Eczematous Disorders*. Boca Raton, Florida: CRC Press/ Taylor & Francis Group; 2014:25–38.
4. Rudikoff D, Lee D, Cohen SR. Clinical aspects and differential diagnosis of atopic dermatitis. In: Rudikoff D, Cohen SR, Scheinfeld N, Eds. *Atopic Dermatitis and Eczematous Disorders*. Boca Raton, Florida: CRC Press/Taylor & Francis Group; 2014:39–76.
5. Abuabara K, Margolis D, Langan S. The long-term control of atopic dermatitis. *Dermatol Clin.* 2017;35:317–326.
6. Rencic A, Cohen BA. Prominent pruritic periumbilical papules: a diagnostic sign in pediatric atopic dermatitis. *Pediatr Dermatol*. 16(6):436–438.
7. Malik K, Heitmiller KD, Czanowicki T. An update on the pathophysiology of atopic dermatitis. *Dermatol Clin.* 2017;35:283–289.
8. Rudikoff D, Bos JD. Pathophysiology of atopic dermatitis and atopiform dermatitis. In: Rudikoff D, Cohen SR, Scheinfeld N, Eds. *Atopic Dermatitis and Eczematous Disorders*. Boca Raton, Florida: CRC Press/ Taylor & Francis Group; 2014:107–144.
9. Renert-Yuval Y, Guttman-Yassky E. New treatments for atopic dermatitis targeting beyond IL-4/ IL-13 cytokines. *Ann Allergy Asthma Immunol*.

2020;124(1):28–35.
10. Del Rosso JQ. More from the pipeline of clinical research on selected systemic therapies for atopic dermatitis. *J Clin Aesthet Dermatol.* 2019;12(5): 49–53.
11. Lee DE, Clark AK, Tran KA, et al. New and emerging targeted systemic therapies: a new era for atopic dermatitis. *J Dermatolog Treat*. 2018 Jun;29(4): 364–374.
12. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol.* 2012;83(12):1583–1590.
13. Schett G, Sloan VS, Stevens RM, Schafer P. Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases. *Ther Adv Musculoskelet Dis.* 2010;2(5):271–278.
14. Soto FJ, Hanania NA. Selective phosphodiesterase-4 inhibitors in chronic obstructive lung disease. *Curr Opin Pulm Med.* 2005;11(2):129–134.
15. Dong C, Virtucio C2, Zemska O, et al. Treatment of skin inflammation with benzoxaborole phosphodiesterase inhibitors: selectivity, cellular activity, and effect on cytokines associated with skin inflammation and skin architecture changes. *J Pharmacol Exp Ther.* 2016;358(3):413–422.
16. Jarnagin K, Chanda S, Coronado D, et al. Crisaborole topical ointment, 2%: a nonsteroidal, topical, anti-inflammatory phosphodiesterase-4 inhibitor in clinical development for the treatment of atopic dermatitis. *J Drugs Dermatol*. 2016;15(4):390–396.
17. Hanifin JM, Chan SC, Cheng JB, et al. Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis. *J Invest Dermatol.* 1996;107(1):51–56
18. Guttman-Yassky E, Hanifin JM, Boguniewicz M, et al. The role of phosphodiesterase 4 in the pathophysiology of atopic dermatitis and the perspective for its inhibition. *Exp Dermatol.* 2019 Jan;28(1):3–10.
19. Chan SC, Li SH, Hanifin JM. Increased interleukin-4 production by atopic mononuclear leukocytes correlates with increased cyclic adenosine monophosphate-phosphodiesterase activity and is reversible by phosphodiesterase inhibition. J Invest Dermatol. 1993;100(5):681–684.
20. Tom WL, Van Syoc M, Chanda S, Zane LT. Pharmacokinetic profile, safety, and tolerability of crisaborole topical ointment, 2% in adolescents with atopic dermatitis: an open-label phase 2a study. *Pediatr Dermatol*. 2016;33(2):150–159.
21. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol*. 2016;75(3):494–503.
22. Callender VD, Alexis AF, Stein Gold LF, et al. Efficacy and safety of crisaborole ointment, 2%, for the treatment of mild-to-moderate atopic dermatitis across racial and ethnic groups. *Am J Clin Dermatol.* 2019;20(5):711–723.
23. Ständer S, Yosipovitch G, Bushmakin AG, et al. Examining the association between pruritus and quality of life in patients with atopic dermatitis treated with crisaborole. *J Eur Acad Dermatol Venereol.* 2019;33(9):1742–1746.
24. Bissonnette R, Pavel AB, Diaz A, et al. Crisaborole and atopic dermatitis skin biomarkers: An intrapatient randomized trial. *J Allergy Clin Immunol.* 2019;144(5):1274–1289.
25. Guttman-Yassky E, et al. Improvement in skin inflammation and barrier function biomarkers with crisaborole treatment in atopic dermatitis. Poster presented at 24th World Congress of Dermatology, Milan, Italy, June 2019.
26. Schlessinger J, Shepard JS, Gower R, et al. Safety, effectiveness, and pharmacokinetics of crisaborole in infants aged 3 to < 24 months with mild-to-moderate atopic dermatitis: a Phase IV open-label study (CrisADe CARE 1). *Am J Clin Dermatol.* 2020;21: 275–284.
27. Merk HF. The aryl hydrocarbon receptor as the target structure for new drugs in psoriasis and atopic dermatitis. *Hautarzt*. 2019;70(12):942–947.
28. Di Meglio P, Duarte JH, Ahlfors H, et al. Activation of the aryl hydrocarbon receptor dampens the severity of inflammatory skin conditions. *Immunity*. 19;40(6):989–1001.
29. Furue M, Hashimoto-Hachiya A, Tsuji G. Aryl hydrocarbon receptors in atopic dermatitis and psoriasis. *Int J Mol Sci.* 2019;20(21). pii: E5424.
30. Peppers J, Paller AS, Maeda-Chubachi T, et al. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. *J Am Acad Dermatol.* 2019;80(1):89-98.
31. Kontzias A, Kotlyar, A, Laurence, et al. Jakinibs: a new class of kinase inhibitors in cancer and autoimmune disease. *Curr Opin Phamacol.* 2012;12(4):464–470.
32. Norman P. Selective JAK inhibitors in the development of rheumatoid arthritis. *Expert Opin Investigat Drugs.* 2014;23(8):1067–1077.
33. Vaddi K, Sarlis NJ, Gupta V. Ruxolitinib, an oral JAK1 and JAK2 inhibitor in myelofibrosis. *Expert Opin Pharmacother.* 2012;13(16):2397–2407.
34. 33 Zerbini CA, Lomonte AB. Tofacitinib for treatment of rheumatoid arthritis. *Exp Rev Clinic Immunol.* 2012;8(4):319–331.
35. Schwartz DM, Bonelli M, Gadina M, et al. Type I/ Type II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol.* 2016;12(1):25–36.
36. Babon JJ, Lucet IS, Murphy JM, et al. The molecular regulation of Janus kinase (JAK) activation. *Biochem J.* 2014;462(1):1–13.
37. Damsky W, King BA. JAK inhibitors in dermatology: the promise of a new drug class. *J Am Acad Dermatol.* 2017;76(4):736–744.
38. Cotter, D, Schairer, D, Eichenfield, L. Emerging therapies for atopic dermatitis: JAK inhibitors. *J Am Acad Dermatol.* 2018;78(3):S53–S62.
39. Relke N, Gooderham M. The use of Janus kinase inhibitors in vitiligo: a review of the literature. *J Cutan Med Surg.* 2019;23(3):298–306.
40. Liu LY, Strassner JP, Refat MA, et al. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J Am Acad Dermatol.* 2017;77(4):675–682.
41. Crowley EL, Fine SC, Katipunan KK, et al. The use of Janus kinase inhibitors in alopecia areata: a review of the literature. *J Cutan Med Surg.* 2019;23(3): 289–297.
42. Tegtmeyer K, Zhao J1 Maloney NJ2. Off-label studies on tofacitinib in dermatology: a review. *J Dermatolog Treat.* 2019 Oct 3:1–11.
43. Solimani F, Meier K, Ghoreschi K. Emerging topical and systemic JAK inhibitors in dermatology. *Front Immunol.* 2019;10:2847.
44. Hosking AM, Juhasz M, Mesinkovska NA. Topical Janus kinase inhibitors: a review of applications in dermatology. *J Am Acad Dermatol.* 2018;79(3): 535–544.
45. Kim BS, Howell MD, Sun K. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol.* 2020 Feb;145(2):572–582.
46. Bissonnette R, Papp KA, Poulin Y, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol.* 2016;175(5): 902–911. JCAD